January 2017

Racial Disparities In Renal Cell Carcinoma: A Single Payer Healthcare Experience

Abiodun Mafolasire
Yale University

RACIAL DISPARITIES IN RENAL CELL CARCINOMA: A SINGLE PAYER HEALTHCARE EXPERIENCE.

A Thesis Submitted to the

Yale University School of Medicine

In Partial Fulfillment of the Requirements for the

Degree of Doctor of Medicine

By

Abiodun Mafolasire

2017

RACIAL DISPARITIES IN RENAL CELL CARCINOMA: A SINGLE PAYER HEALTHCARE EXPERIENCE. Abiodun Mafolasire, Xiaopan Yao, Cayce Nawaf, Alfredo Suarez-Sarmiento, Wong-Ho Chow, Wei Zhao, Douglas Corley, Jonathan N. Hofmann, Mark Purdue, Adebowale J. Adeniran, (Sponsored by) Brian Shuch. Department of Urology, Yale University School of Medicine, New Haven, CT.

Introduction: Significant racial disparities in survival for renal cell carcinoma (RCC) exist between whites and blacks. Differences in access to care and comorbidities are possible contributors. To investigate if racial disparities persist when controlling for access to care, we analyzed data from a single payer healthcare system.

Methods: As part of a case-control study within the Kaiser Permanente Northern California system, pathologic and clinical records were obtained for RCC cases (2,152 white, 293 black) diagnosed from 1998 to 2008. Patient demographics, comorbidities, tumor characteristics, and treatment status were compared between whites and blacks. Overall survival and disease specific survival (DSS) were calculated by the Kaplan-Meier method. A Cox proportion hazards model was used to estimate the independent associations of race, comorbidity, and clinico-pathologic variables with DSS.

Results: Compared to whites, blacks were diagnosed at a younger age (median 62 vs. 66 years, $p<0.001$), were more likely to have papillary RCC (15% vs. 5.2%, $p<0.001$), and had similar rates of surgical treatment (78.8% vs. 77.9%, $p=0.764$). On multivariate analysis, advanced AJCC stage, lack of surgical treatment, larger tumor size, and higher grade were predictors of worse DSS. Race was not an independent predictor of survival.

Conclusions: Within a single healthcare system, we observed differences in characteristics of black and white patients with RCC; black patients had different comorbidities, were younger, and had decreased tumor stage. However, unlike other series, race was not an independent predictor of DSS, suggesting that survival differences in large registries may result from barriers to healthcare access and/or comorbidity rather than disease biology.

ACKNOWLEDGEMENTS

I would like to express my gratitude to my supervisor, Dr. Brian Shuch without whom this project would not have come to fruition. His experience, guidance, understanding, and particularly patience were instrumental at every step of this project. Without a doubt, I gained a lot from his vast experience and extensive knowledge in many areas. A very special thanks also goes to Dr. Adeniran. His guidance and support as an advisor and mentor were vital to me.

I would also like to thank my family whose life-long support, belief and understanding shaped me into who I am. My thanks will not be complete without mentioning my two children - Adrian and Adrienne. Thank you both for your sacrifices. Finally, I like to thank my late father, Olatunji Mafolasire. I am saddened that you are not around to witness the culmination of all the years of hard work but heartened by the courage with which you lived to the end and the valuable life advice you have given me all through the years.

This study was partially supported by stipends from Yale School of Medicine Office of Student Research and has been published in *Cancer medicine* 2016 Aug 1;5(8):2101-8. DOI: 10.1002/cam4.755

TABLE OF CONTENTS

INTRODUCTION

Renal cell carcinoma (RCC) is a group of tumors arising from parenchyma of the kidney. RCC is the seventh most common malignancy in the United States with approximately 60,000 new cases and 14,000 deaths estimated for 2016. It accounts for 95% of kidney cancers diagnosed in the United States.[1]

Rising RCC Incidence over the Last 30 Years

The incidence of RCC has been increasing in the United States over the last few decades.[2-5] This trend was first reported in a study published at the end of the last century looking at rates of RCC from 1975 to 1995 using population-based data from 10 cancer registries that are part of the National Cancer Institute (NCI)'s Surveillance Epidemiology, and End Results (SEER) program. Chow et al found that incidence of RCC had increased across all racial groups with the greatest increase occurring in localized tumors[2]. Another study using population-based data from 13 cancer registries that are part of the SEER program, found that age-adjusted incidence rates of RCC nearly tripled from 6.5/100 000 person-years in 1975 to 17.1/100 000 person-years to 2009. More recent data shows the trend of rising in incidence has not abated with age-adjusted incidence of RCC increasing annually by of 2.80% from 2000 to 2009 which is similar to rate of 2.76% from 1975 to 1999.[4]

What is driving this increase in incidence? There is consensus that increased incidental detection from an expanding role of diagnostic imaging is a significant contributor.[2,4] As noted by both SEER-based studies[2,4], that time period also saw a concurrent rise in the use

of diagnostic imaging[6,7]. Citing data from Medicare beneficiaries, Chow et al found a 76% increase in CT scans or MRI between 1986 and 1994.[2] The use of CT scans in Medicare patients is estimated to have grown at 8% annually from 1980 to 2006 with abdominal imaging growing at an even faster annual rate of 9%.[6] Internationally, developed nations in Western Europe and America have also seen a rising RCC incidence, now approaching double that of less developed regions of the world in Africa and Latin America where imaging use is not as prevalent.[8] This further bolsters the argument that an association exists between increased use of cross-sectional imaging and the amount of RCC diagnosed.

However, rising incidental detection from expanding use of imaging studies may not explain all of the increase in recent decades. Expectedly, the detection of small, localized tumors increased with more frequent imaging, but locally advanced and metastatic tumors have also consistently risen in the interval period considered[2,4]. This suggests that while increased use of imaging modalities may have contributed to increased incidental detection, it does not wholly explain it. Increases in prevalence of RCC risk factors might be a contributor to these trends.

RCC Risk Factors

Known epidemiologic risk factors predisposing for RCC including smoking, male gender, chronic kidney disease (CKD), hypertension, and obesity[9-15]. Some of these risk factors differ among racial group and may be contributing to the differences in epidemiological trends.[14,16] Hypertension and chronic kidney disease are two well established risk factors that have racial disparity in both prevalence and possibly how

they influence RCC. In general, both are more common in blacks. Hypertension has been shown to increase the risk of RCC in blacks more than whites, with the greatest risk occurring in those with uncontrolled hypertension[11]. CKD has similarly been shown to have a disparate racial influence on RCC with the association being stronger among blacks than other racial groups[16].

Obesity rates have been increasing in the US over the last three decades with 35.0% of men and 40.4% of women now considered obese. Rates for black males and females are higher at 38% and 57.2% respectively.[17] High body-mass index (BMI) is an established risk factor for RCC.[18,19] A meta-analysis of 21 cohort studies with a combined study participants of over 9 million and over 15,000 RCC cases across three continents found a dose-dependent relationship between BMI and RCC. Risk for RCC increased by 4% increased for every 1kg/m^2 increase in BMI.

Epidemiological RCC Trends in Blacks

In the United States, an emerging body of studies suggests there are some trends peculiar to black patients diagnosed with RCC. Significantly, black patients tend to be diagnosed at a younger age, have a faster rising incidence rate, are disproportionately diagnosed with papillary RCC subtype, overall have more favorable tumor pathology at diagnosis and appear to have worse survival outcomes.[20-23]

Incidence of RCC in blacks rising faster than rest of the population

The increased incidence of RCC in the United States has not been uniform across racial groups. RCC has increased faster in blacks than among non-blacks. Chow's SEER based data showed that over a 20 year period from 1975 to 1995, RCC incidence grew annually by 3.9% among black men compared to 2.3% among white men, and 4.3% in black women compared 3.1% among white women.[2] Reasons for this growth disparity are unclear with disparate racial prevalence of risk factors such as obesity, chronic kidney disease (CKD) being possible contributing factors[16].

Blacks have more papillary RCC

The distribution of histologic RCC subtypes is well-characterized with clear cell accounting for 70-80% and papillary RCC accounting for 15-20%.[24,25] However, recent data suggests that black patients diagnosed with RCC disproportionately present with the papillary subtype when compared to other racial groups in the US. There is evidence that papillary subtype has more favorable outcomes in the general population[26-28]. This trend among blacks was first noted in large-scale population wide studies published within the last decade. In a study of nearly 40,000 patients from national cancer registries, blacks were diagnosed with papillary RCC at nearly three times the rates of whites (12.5% vs 4.3%). In a larger study using of nearly 50,000 patients from 18 population-based SEER registries across the country, blacks were four times more likely to have the papillary RCC subtype than whites.[29] It should be noted that these large studies do not included pathologic review, although Shuch et al showed that SEER pathologic diagnosis are mostly accurate.[30]

Recent studies from single-center academic medical institutions reports similar findings. In a study of 1532 patients (1403 whites, 129 white) done at Vanderbilt University Medical Center with a staff surgical pathologist reviewing and confirming the diagnosis, blacks were diagnosed with papillary RCC at nearly 3 times the rates of white (35.7% vs 13.8%). Conversely, clear cell subtype was only diagnosed in 39.5% of blacks compared to 75.9% of whites.[20] In a similar study another done at Duke, another tertiary academic medical center, looking at 1467 patients (359 blacks, and 1108 non-blacks) who underwent surgical resection for RCC, black patients were diagnosed with papillary RCC at almost greater nearly 4 times the rates (40.8% vs 11.6%)[21].

Blacks are diagnosed younger and at an earlier stage

The median age of kidney cancer is approximately 64 years of age with a fairly wide age distribution. Black patients are diagnosed at a younger age compared to white patients. In the SEER-based study referenced earlier, 66.7% of RCC diagnosed in blacks were in patients younger than 65 years old compared to only 56.7% of whites.[9] In a study of nearly 40, 000 patients from state of California's cancer registry from 1988 to 2004, the median age for black patients at diagnosis was a 5 years less than white patients[31]. Smaller single-institution studies from tertiary academic hospitals across the US have also found similar trends[20,21]. Reasons for this trend have not been clearly elucidated.

Blacks have more favorable pathology

Black patients are more likely to have localized tumors, less likely to have regionally advanced and distant metastasis. These trends have been consistently present in using population-based data sets from across the country and multiple single-institution data in

which tumor pathology by race was included. In Chow's SEER study, 66.7% of RCC in black patients were localized compared to 61.9% in white. In another study of over 12,000 patients from 9 SEER cancer registries, black patients, compared to whites, were more likely to have localized RCC localized (72.6% vs 66.9%), less likely to have metastatic disease (14.6% vs 15.3%).[9] In the single institution cohort studied by Qi and colleagues, blacks, compared to non-blacks, had higher proportion of lower staged tumors, T1a (52.2 vs 42.7), T1b (23.4% vs 20.8%) and lower proportions of higher staged tumors T3 (14.1% vs 23.5%). They also had more localized disease (83% vs 71%) and fewer locally advanced (11% vs 16%) and metastatic disease (6% vs 13%).[21]

Blacks seem to have worse survival outcomes

Most significantly is the worse survival outcome for blacks patients with RCC noted in large population-wide studies. Two studies published within the last decade using population-wide databases found that compared to whites, black patients with RCC had worse outcomes.[3,22,31] While black patients present at an earlier disease stage, at a younger age, and with more favorable pathology, paradoxically, survival appears to be worse.[3,22] Even when controlling for treatment and various prognostic factors such as stage, tumor size, and grade, a disparity in relative survival still persists between blacks and whites with kidney cancer.[3]

Unfortunately in the US, access to health care significantly differs by race, which may largely account for the observed difference in cancer-related outcomes due to treatment barriers. Besides possible differences in tumor biology, this could account for the apparent worse survival in black patients with RCC. Data from National Cancer Institute's

Surveillance Epidemiology and End Results (SEER) program demonstrates that blacks are less likely to undergo definitive surgical therapy (nephrectomy) [22,32,33]. The decreased rate of nephrectomy may be influenced by greater pre-existing comorbidities in blacks[22]. However, even when controlling for treatment, other studies have found blacks have worse outcome[3].

Analyses of survival outcomes using large registries may be unable to account for barriers to care and lead to an improper conclusion that those survival disparities are related to tumor biology. Studies have shown that differences in cancer-related outcomes may disappear when evaluated in single health care system[34,35]. By using a single health care payer database, we evaluate whether racial survival differences exist while controlling for demographics, tumor characteristics, comorbidities, and treatment in a system where all patients should receive equivalent care.

STATEMENT OF PURPOSE

The goal of this study is to comprehensively assess epidemiologic, clinical, pathological and survival outcomes between black and white patients diagnosed with RCC who received care within an integrated single-payer health care system.

Hypothesis 1: We theorized that racial disparity in survival noted between black and white patients in population based studies may largely be explained away by barriers and/or access to care. These disparity would decrease or disappear when survival analyses are performed for a cohort with equivalent access to and quality of care as may be found in an integrated single healthcare system.
Specifically, we tested the hypothesis that there will be no difference in disease specific survival outcomes between black and white patients with RCC treated within that system.

Hypothesis 2: Blacks patients with RCC in this cohort of this study will disproportionately present with papillary subtype when compared to whites, as has been similarly showing in other datasets.

Hypothesis 3. We hypothesize that compared to whites, clinico-pathologic (blacks diagnosed at a younger age and with more favorable pathology) of black patients will be in concordance with previously noted trends found in multiple nationwide datasets

MATERIALS AND METHODS

Study Design

To evaluate racial disparities between whites and blacks in an integrated-managed care system, we conducted an investigation among RCC cases from a nested case-control study in the Kaiser Permanente Northern California (KPNC) health system[16]. Patients receiving care from KPNC were included in our study if they had been diagnosed with RCC (International Classification of Diseases for Oncology, 3rd Edition, site code C64.9) between 1998 and 2008. The demographic data were obtained from membership databases which include age, race/ethnicity (self-described) and gender.

The cancer data were obtained from Kaiser Permanente Cancer Registry, which reports directly to the Surveillance, Epidemiology, and End Results program. Cancer location, tumor size, T stage, grade, AJCC stage, histology, treatment data, and survival were recorded for the registry using chart review. Comorbidity data (BMI, smoking history, hypertension, diabetes, CKD, any medical renal disease, and anemia), were defined using international classification of disease (version 9) coding associated with visits. Tumor AJCC stage was re-coded in accordance with current 7th edition guidelines[36]. Vital status and the last follow-up date was available until December 31, 2013. The cause and date of death were assigned using a combination of cancer registry data and a mortality registry that concatenates state and federal mortality files including primary cause of death from California death certifications.

Statistical Analysis

All analyses were performed using SAS 9.3 (SAS Institute, Inc., Cary, NC) and R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria). For patient clinical characteristics, continuous variables are presented as median (range) and categorical ones as frequency with relative percentage. Group comparisons between blacks and whites were performed with the use of Fisher's exact test or chi-square tests for categorical variables and Mann–Whitney U tests for continuous variables, as appropriate.

Overall survival (OS) was measured from the date of diagnosis to the date of death (based on the death certificate), alive patients are censored at the date of last follow-up date. Disease-specific survival (DSS) was measured from the date of diagnosis to the date of death caused by disease; both alive patients and patients who died due to other causes are censored at the last follow-up date and death date respectively. The association of survival with clinical and prognostic factors was tested using the log-rank test. Prognostic factors that were significantly associated with DSS survival on univariate analysis and clinically relevant factors were included in a Cox proportional-hazards model for multivariate analysis. Statistical significance was considered for p values ≤ 0.05.

My involvement

Under supervision of Dr. Shuch, I formulated the research questions and study design. I cleaned up the preliminary data file received by removing extraneous information, recoding variables as needed, distilling out pertinent data and optimizing dataset for statistical analysis. Using the current AJCC 7th edition guidelines and under the direction of Dr. Shuch, I went through the entire data and individually determined the appropriate

tumor staging. Patients with existing older AJCC staging were updated to the 7th edition. AJCC 7th edition staging were deduced from available pathologic data and coded accordingly for those with missing entries. I also did all of the preliminary statistical analysis including group comparisons between blacks and whites using the Fisher's exact test or chi-square tests for categorical variables and Mann–Whitney U tests for continuous variables, as well as the univariate and multivariate survival analysis, as appropriate. Final statistical analysis presented in the published manuscript and this thesis were done in conjunction with Yale Center for Analytical Sciences (YCAS)

RESULTS

Patient and Disease Characteristics

A total of 2,445 patients were included in this study, of which 2,152 (88.0%) were white and 293 (12.0%) were black. The clinical and pathological features for entire cohort are shown in Table 1. The median age of diagnosis for blacks was significantly lower than for whites (62 vs 66 years, respectively, p<0.001) (Table 1). Compared to whites, a higher proportion of black patients had a history of hypertension (64.9% vs 50.1%, p<0.001), chronic kidney disease (10.2% vs 0.7%, p = <0.001) and anemia (10.2% vs 0.7%, p = <0.001). There were no significant racial differences in BMI, diabetes, or smoking history.

Tumor characteristics significantly differed between whites and blacks. Papillary histology was more frequently diagnosed in blacks than in whites (15.0% vs 5.1%, p = <0.001). At diagnosis, black patients presented less frequently with metastasis (15.7% vs 22.1%, p = 0.012) and had a greater frequency of localized disease (AJCC stage I/II) (70.2% vs 62.2%, p = 0.008). Although, not reaching statistical significance, blacks tended to have smaller sized tumors (4.4 cm vs 5.1 cm, p = 0.066). No racial differences were observed in tumor grade and nodal status. No statistical difference was found in the rate of surgical treatment between whites and blacks (77.9% vs. 78.8%, p = 0.764).

Table 1: Demographic, clinical, pathologic, outcomes data of white and black patients with RCC who received care with Kaiser Permanente Northern California from 1998–2008

Variable	Blacks (N=293)	Whites (N=2152)	*p* value
Age at diagnosis (years)			<.001
Median	62	66	
Gender			0.007
Male	166 (56.7%)	1392 (64.7%)	
Female	127 (43.3%)	760 (35.3%)	
BMI*			0.553
< 25	9 (15%)	95 (20.8%)	
25 to 30	24 (40%)	163 (35.7%)	
> 30	27 (45%)	199 (43.5%)	
Smoking History			0.263
Yes	81 (27.65%)	530 (24.6%)	
No	212 (72.4%)	1622 (75.4%)	
Hypertension			<0.001
Yes	190 (64.9%)	1077 (50.1%)	
No	103 (35.2%)	1075 (49.9%)	
Diabetes			0.094
Yes	58 (19.8%)	343 (15.9%)	
No	235 (80.2%)	1809 (84.1%)	
CKD			<0.001
Yes	30 (10.2%)	15 (0.7%)	
No	263 (89.8%)	2137 (99.3%)	
Renal Disease			<0.001
Yes	35 (11.9%)	49 (2.3%)	
No	258 (88.1%)	2103 (97.7%)	
Anemia			<0.001
Yes	52 (17.7%)	181 (8.4%)	
No	241 (82.3%)	1971 (91.6%)	
Tumor size			0.066
Median	4.4	5.1	
Histologic subtype			<0.001
Clear cell	208 (71.0%)	1829 (85.0%)	
Papillary	44 (15.0%)	111 (5.2%)	
Chromophobe	12 (4.1%)	56 (2.6%)	
Others	29(9.9%)	156 (7.3%)	
Tumor Grade (850 missing)			0.463
Grade 1	30 (15.2%)	198 (14.2%)	
Grade 2	98 (49.7%)	648 (46.4)	
Grade 3	59 (29.9%)	441 (31.5%)	
Grade 4	10 (5.1%)	111 (7.9%)	
T Stage (193 missing)			0.053
T1/T2	215 (77.6%)	1424 (72.1%)	

T3/T4	62 (22.4%)	551 (27.9%)	
N Stage (1 missing)			0.640
N0/Nx	284 (96.9%)	2095 (97.4%)	
N+	9 (3.1%)	56 (2.6%)	
M Stage			0.012
M0/Mx	247 (84.3%)	1677 (77.9%)	
M+	46 (15.7%)	475 (22.1%)	
AJCC Staging (15 missing)			0.008
Stage I/II	205 (70.2%)	1330 (62.2%)	
Stage III/IV	87 (29.8%)	808 (37.8%)	
Treatment Option			0.723
Surgery	231 (78.8%)	1677 (77.9%)	
No surgery	62 (21.2%)	475 (22.1%)	
Vital Status			0.202
Alive	152 (51.9%)	1031 (47.9%)	
Dead	141 (48.1%)	1121 (52.1%)	
Death from RCC			0.033
Alive	152 (51.9%)	1031 (47.9%)	
Dead from other cause	64 (21.8%)	626 (29.1%)	
Dead from RCC	77 (26.3%)	495 (23.0%)	

* BMI data only available for patients enrolled from 2005 - 2008

In patients with clear cell subtype, black patients were diagnosed at a younger median age (63 vs. 66, $p = 0.003$). Blacks with clear cell RCC were less likely to be male (54.3% vs 63.8%, $p = 0.008$) (Table 2). Compared to whites, black patients with clear cell RCC were also more likely to have been diagnosed with hypertension (64.4% vs 49.9%, $p < 0.001$), over ten times more likely to have been diagnosed with chronic kidney disease (9.6% vs 0.7%, $p < 0.001$), and twice as likely to have had anemia (16.3% vs 8.4%, $p < 0.001$) (Table 2) There was no statistical difference between blacks and whites with clear cell RCC in tumor grade, size, nodal, or metastatic status. There was also no statistical difference between blacks and whites in the percentage of patients that underwent surgery (71.6% vs 76.0%, $p = 0.173$) (Table 2)

Table 2: Demographic, clinical, pathologic, outcomes data of white and black patients with clear cell RCC and received care with Northern California Kaiser Permanente General from 1998–2008

Subcategory	Blacks ccRCC N=208	Whites ccRCC N=1829	*p* value
Age			0.003
Median	63	66	
Gender			0.008
Male	113 (54.3%)	1166 (63.8%)	
Female	95 (45.7%)	663 (36.2%)	
BMI*			0.824
< 25	6 (16.2%)	75 (19.7%)	
25 to 30	15 (40.5%)	138 (36.2%)	
>30	16 (43.2%)	168 (44.1%)	
Smoking History			0.610
Yes	54 (26.0%)	445 (24.3%)	
No	154 (74.0%)	1384 (75.7%)	
Hypertension			<0.001
Yes	134 (64.4%)	913 (49.9%)	
No	74 (34.6%)	916 (50.1%)	
Diabetes			0.072
Yes	45 (21.6%)	305 (16.7%)	
No	163 (78.4%)	1524 (83.3%)	
CKD			<0.001
Yes	20 (9.6%)	12 (0.7%)	
No	188 (90.4%)	1817 (99.3%)	
Any renal disease			<0.001
Yes	22 (10.6%)	42 (2.3%)	
No	186 (89.4%)	1787 (97.7%)	
Anemia			<0.001
Yes	34 (16.3%)	153 (8.4%)	
No	174 (83.7%)	1676 (91.6%)	
Tumor size (cm)			0.118
Median	4.0	5.1	
Tumor Grade			0.396
Grade 1	19 (14.7%)	174 (14.7%)	
Grade 2	71 (54.2%)	558 (47.2%)	
Grade 3	35 (26.7%)	365 (30.9%)	
Grade 4	6 (4.6%)	84 (7.1%)	
T stage			0.3833
T1/T2	144 (74.6%)	1197 (71.6%)	
T3/T4	49 (25.4%)	474 (28.4%)	
N Stage			0.882
N0/Nx	203 (97.6%)	1787 (97.8%)	
N+	5 (2.4%)	41 (2.2%)	
M Stage			0.445
M0/Mx	165 (79.3%)	1408 (77.0%)	
M+	43 (20.7%)	421 (23.0%)	
AJCC Stage			0.347
Stage I/II	135 (65.2%)	1123 (61.9%)	
Stage III/IV	72 (34.8%)	692 (38.1%)	
Surgery			0.173
Yes	149 (71.6%)	1390 (76.0%)	
No	59 (28.4%)	439 (24.0%)	

* BMI data only available for patients enrolled from 2005 - 2008

In comparing black and white patients diagnosed with papillary RCC, the median age at diagnosis for black patients was also younger (57.5 vs 64, $p = 0.003$) with the racial age gap being larger than clear cell RCC. Although not reaching statistical significance, tumor size in black patients with papillary renal tumors were larger than white patients (5.35 cm vs 4.2 cm, $p = 0.063$) (Table 3).

Table 3: Demographic, clinical, pathologic, outcomes data of white and black patients with papillary RCC and received care with Northern California Kaiser Permanente General from 1998–2008

Subcategory	Blacks papRCC N=44	Whites papRCC N=101	*p* value
Age			0.003
Median	57.5	64	
Gender			0.528
Male	32 (72.7%)	87 (78.4%)	
Female	12 (27.3%)	24 (21.6%)	
BMI*			0.188
< 25	2 (11.1%)	12 (28.6%)	
25 to 30	7 (38.9%)	18 (42.9%)	
>30	9 (50%)	12 (28.6%)	
Smoking History			0.272
Yes	20 (45.45%)	39 (35.1%)	
No	24 (54.55%)	72 (64.9%)	
Hypertension			0.095
Yes	33 (75%)	66 (59.5%)	
No	11 (25%)	45 (40.5%)	
Diabetes			0.595
Yes	7 (15.9%)	13 (11.7%)	
No	37 (84.1%)	98 (88.3%)	
CKD			0.006
Yes	7 (15.9%)	3 (2.7%)	
No	37 (84.1%)	108 (97.3%)	
Any renal disease			0.002
Yes	9 (20.45%)	4 (3.6%)	
No	35 (79.55%)	107 (96.4%)	
Anemia			0.088
Yes	8 (18.2%)	9 (8.1%)	
No	36 (81.2%)	102 (91.9%)	
Tumor size			0.063
Median	5.35	4.2	
Tumor Grade			0.311
Grade 1	7 (21.2%)	12 (15.8%)	
Grade 2	14 (42.4%)	45 (59.2%)	
Grade 3	12 (36.4%)	18 (23.7%)	
Grade 4	0 (0%)	1 (1.3%)	
T stage			1.000
T1/T2	38 (88.4%)	97 (89%)	

T3/T4	5 (11.6%)	12 (11%)	
N Stage			0.319
N0/Nx	42 (95.5%)	109 (98.2%)	
N+	2 (4.5%)	2 (1.8%)	
M Stage			0.676
M0/Mx	43 (97.7%)	106 (95.5%)	
M+	1 (2.3%)	5 (4.5%)	
AJCC Stage			1.000
Stage I/II	37 (84.1%)	93 (83.8%)	
Stage III/IV	7 (15.9%)	18 (16.2%)	
Surgery			1.000
Yes	42 (95.5%)	105 (94.6%)	
No	2 (4.5%)	6 (5.4%)	

* BMI data only available for patients enrolled from 2005 - 2008

Comparing clinical and demographic data for black patients only, the median age of those diagnosed with papillary RCC was 5.5 years less than black patients diagnosed with clear cell RCC (57.5 vs 63, $p = 0.003$). Blacks with papillary RCC were also more likely to be male (72.7% vs 54.3%, $p = 0.025$), and significantly more likely to have a smoking history (45.5% vs 26%, $p = 0.010$) compared to those with clear cell RCC. (Table 4)

Table 4: Demographic, clinical data of black patients with papillary RCC and clear cell RCC who received care with Northern California Kaiser Permanente General from 1998–2008

Subcategory	Blacks papRCC N=44	Blacks ccRCC N=208	*p* value
Age			0.003
Median	57.5	63	
Gender			0.025
Male	32 (72.7%)	113 (54.3%)	
Female	12 (27.3%)	95 (45.7%)	
BMI*			0.928
< 25	2 (11.1%)	6 (16.2%)	
25 to 30	7 (38.9%)	15 (40.5%)	
>30	9 (50%)	16 (43.3%)	
Smoking History			0.010
Yes	20 (45.45%)	54 (26.0%)	
No	24 (54.55%)	154 (74.0%)	
Hypertension			0.178
Yes	33 (75%)	134 (64.4%)	
No	11 (25%)	74 (35.6%)	
Diabetes			0.394

Yes	7 (15.9%)	45 (21.6%)	
No	37 (84.1%)	163 (78.4%)	
CKD			0.280
Yes	7 (15.9%)	20 (9.6%)	
No	37 (84.1%)	188 (90.4%)	
Any renal disease			0.069
Yes	9 (20.45%)	22 (10.6%)	
No	35 (79.55%)	186 (89.4%)	
Anemia			0.767
Yes	8 (18.2%)	34 (16.35%)	
No	36 (81.2%)	174 (83.65%)	

* BMI data only available for patients enrolled from 2005 - 2008

Survival Analysis

RCC deaths were more frequent in black patients compared to whites (26.3% vs. 23.0%, $p = 0.033$). Median follow-up time for all black patients was 5.5 years compared to 4.5 years for all white patients. Overall, median follow-up time in all the surviving patients was 7.24 years. In the univariate analysis, there was no significant difference in terms of overall survival between black patients and whites ($p = 0.21$) (Figure 1). The median OS time for blacks is 8.47 years with 95% confidence interval (6.86, 11.75) and the median OS for whites is 7.74 years with 95% confidence interval (7.09, 8.43).

Surprisingly, blacks were found to have improved DSS ($p = 0.016$) (Figure 2). The five and ten-year DSS estimates for blacks vs. whites were 78% and 75% vs 71% and 67%, respectively.

Figure 1: Overall Survival (OS) for Black and White patients diagnosed with kidney cancer who received treatment within Northern California Kaiser Permanente General between 1998 - 2008

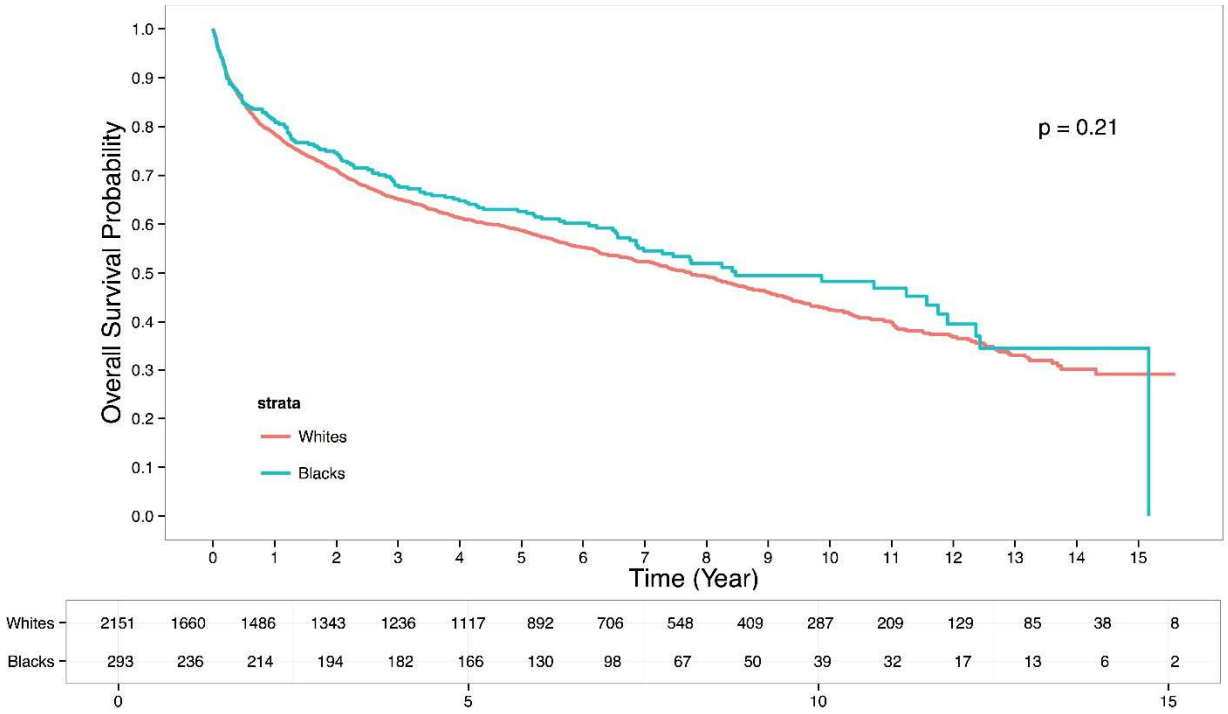
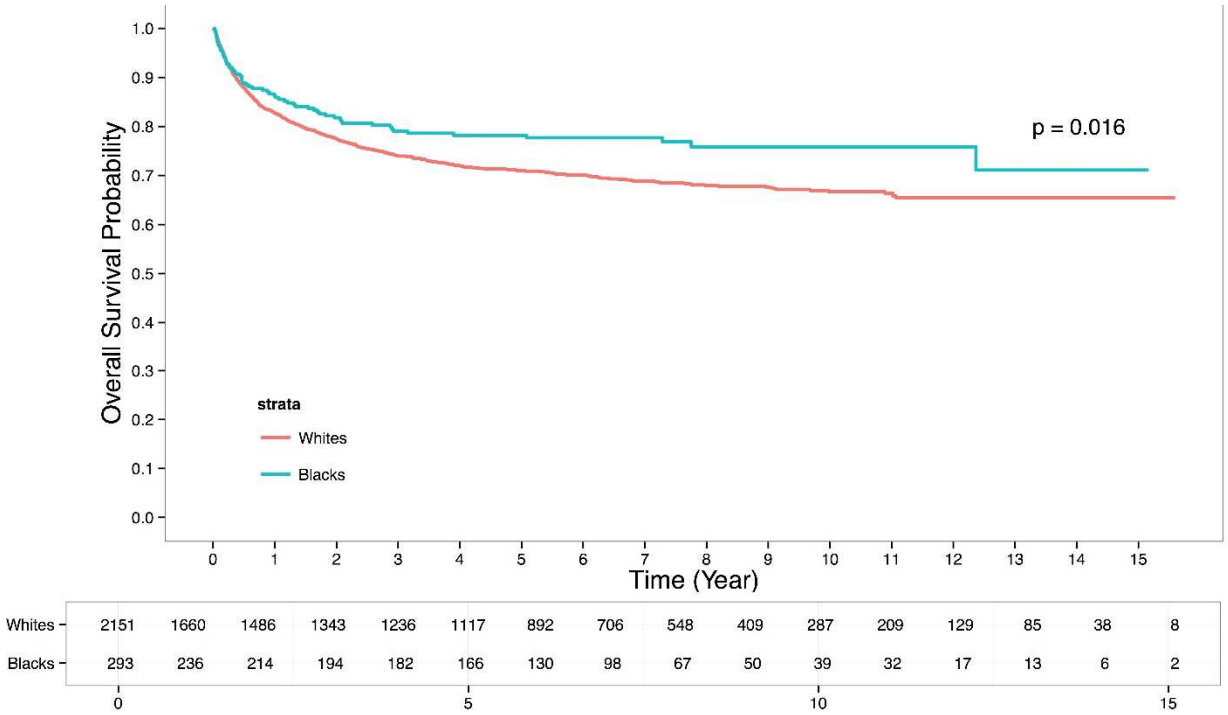
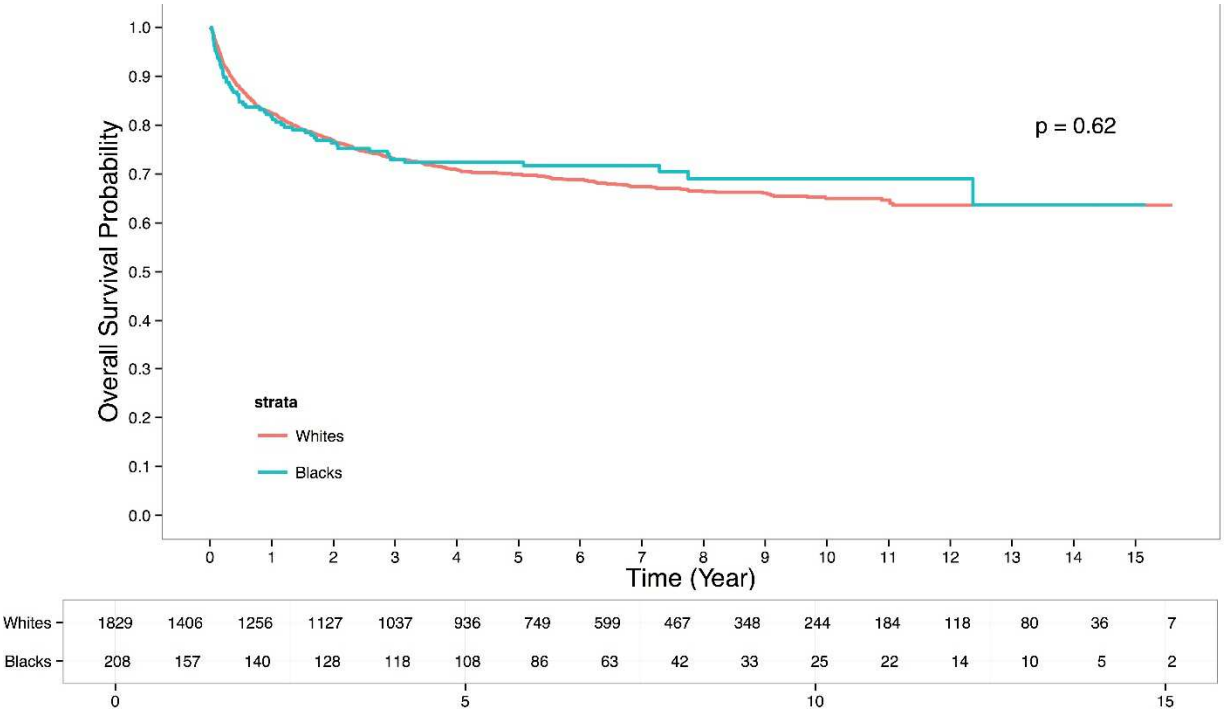


Figure 2: Disease Specific Survival (DSS) for Black and White patients diagnosed with kidney cancer who received treatment within Northern California Kaiser Permanente General between 1998 – 2008



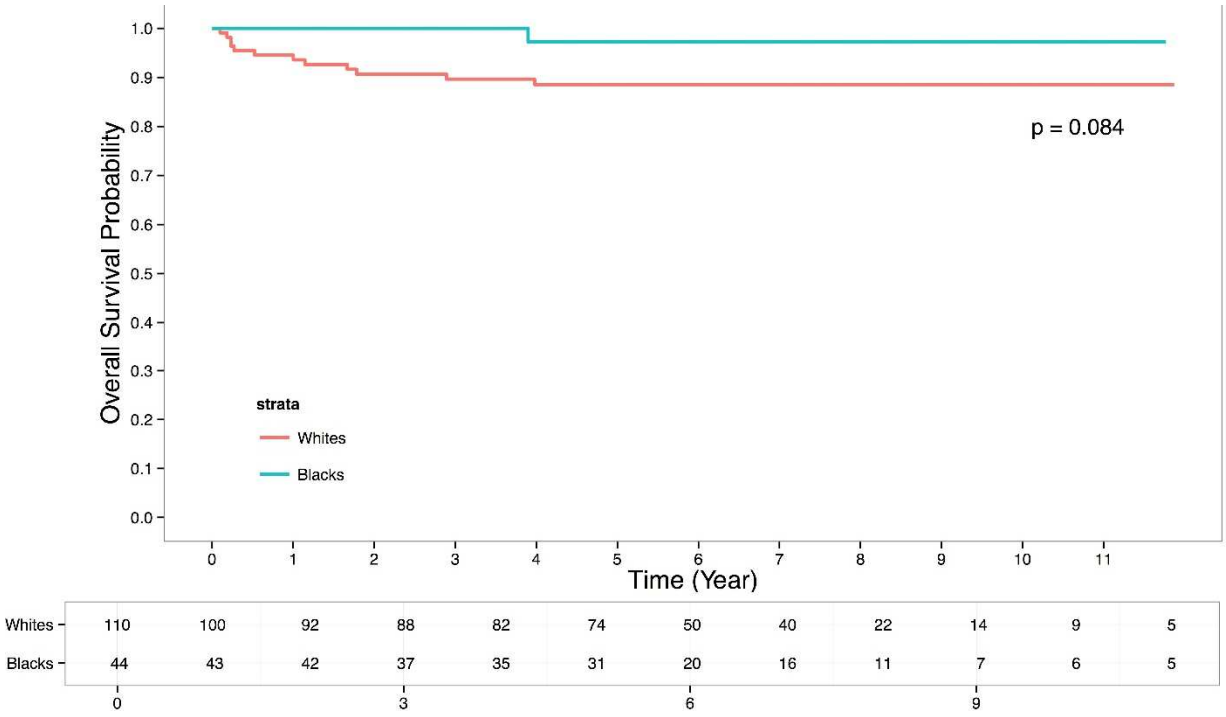
In comparing DSS for the two largest histological subtypes, DSS between black and white patients with clear-cell appear to be nearly identical (Figure 3) with a 5-year survival of 72% for black patients versus 70% for white patients.

Figure 3: Disease Specific Survival (DSS) for Black and White patients diagnosed with Clear-Cell kidney cancer



For papillary RCC, although while statistically not significant, there was a trend for improved DSS for black patients with a 5 year survival of 92% versus 78% for whites (p = 0.084). The survival advantage trends for black patients persisted through 10 years of follow up (Figure 4).

Figure 4: Disease Specific Survival (DSS) for Black and White patients diagnosed with Papillary kidney cancer



In univariate analysis, race, age, AJCC stage, grade, tumor size, histology, and receipt of surgery were found to be predictors of DSS (Table 5). AJCC tumor staging was the most significant predictor of adverse survival with more advanced stages (AJCC stages 3 and 4) carrying much more risk than earlier stages (AJCC stage 1& 2 (HR 15.1, p <0.001). Higher grades were also predictors of worse outcomes with grade 3 and grade 4 tumors carrying 6.92 and 2.92 times the risk of lower grade tumors. (Table 5)

Table 5: Univariate analysis of prognostic clinicopathologic variables for Disease Specific Survival (DSS) in patients with kidney cancer who received care with Northern California Kaiser Permanente General from 1998–2008

Variable	Hazard Ratio (HR)	95% CI	*p* value
Age	1.026	1.02–1.03	<0.001
Gender			0.889
Male	1.00 (ref)		
Female	0.89	0.85–1.55	
Race			0.016
White	1.00 (ref)		
Black	0.73	0.57–0.95	
Smoking History	1.01	0.85–1.20	0.914
Hypertension	1.03	0.89–1.20	0.683
Diabetes	0.95	0.77–1.17	0.607
Anemia	0.86	0.65–1.13	0.285
Renal Disease	0.59	0.34–1.02	0.060
Tumor size (cm)	1.04	1.04–1.05	<0.001
Tumor Grade			<0.001
Grade 1 & 2	1.00 (ref)		
Grade 3	2.92	2.27–3.75	<0.001
Grade 4	6.92	5.05–9.48	
Histological Subtype			0.364
Clear Cell	1.00 (ref)		<0.001
Papillary	0.24	0.14–0.42	<0.001
Others	0.80	0.61–1.04	0.092
AJCC Stage			<0.001
Stage 1 & 2	1.00 (ref)		
Stage 3 & 4	15.5	12.6–18.9	
Treatment Status			<0.001
Surgery	1.00 (ref)		
No Surgery	12.0	10.3–14.1	

In multivariate analysis, only larger tumor size, higher tumor grade, advanced AJCC stage and not being treated with surgery were found to be independent predictors of DSS. Age, histology, and race were no longer associated with DSS (Table 6).

Table 6: Multivariate analysis of prognostic variables for Disease Specific Survival (DSS) in patients with kidney cancer who received care with Northern California Kaiser Permanente General from 1998–2008

Variable	Hazard Ratio (HR)	95% CI	*p* value
Age	1.001		0.896
Gender			0.964
Male	1.00 (ref)		
Female	0.99	0.78–1.27	
Race			0.382
White	1.00 (ref)		
Black	0.82	0.52–1.29	
Renal Disease	1.43	0.52–3.94	0.481
Tumor size (cm)	1.05	1.04–1.06	<0.001
Tumor Grade			<0.001
Grade 1 & 2	1.00 (ref)		
Grade 3	1.86	1.42–2.43	
Grade 4	3.32	2.36–4.69	
Histological Subtype			0.364
Clear Cell	1.00 (ref)		
Papillary	0.72	0.35–1.49	0.378
Others	0.809	0.56–1.15	0.241
AJCC Stage			<0.001
Stage 1 & 2	1.00 (ref)		
Stage 3 & 4	8.63	6.48–11.5	
Treatment Status			<0.001
Surgery	1.00 (ref)		
No Surgery	5.74	4.23–7.81	

DISCUSSION

Using a large single health care system database, we examined the clinico-pathologic characteristics and survival outcomes for black and white patients with renal cell carcinoma and found that while clinico-pathological differences exist between black and white patients, race was not a predictor of disease specific survival. While black patients in univariate analysis appeared to have better disease specific survival, race dropped off as an independent predictor in multivariate analysis. Only well-established prognostic variables such as tumor size, stage, grade, and surgical treatment influenced outcomes. Despite papillary kidney cancer being three times more common in blacks and a more indolent RCC variant, histology did not appear to influence prognosis. Paradoxically, we noted that DSS was significantly improved in black patients prior to adjusting for other prognostic variables. This finding is likely driven by the racial differences observed in epidemiologic and tumor characteristics in black patients including more favorable age at diagnosis, tumor stage, lower incidence of metastatic disease, and smaller tumors.

The lack of a racial survival disparity observed in our study contrasts sharply with several previous studies using large population-wide databases that consistently demonstrated worse survival outcomes for blacks with RCC[3,22,31]. Specifically, in a study of nearly 40,000 patients Chow et al found that black patients were at a survival disadvantage to white patients that could not be explained by era of diagnosis, histological subtype, size and stage of tumors[3]. Their results are consistent with other population-wide RCC survival studies published within the last decade. Whereas Chow et al looked at nationwide data, Stafford et al using statewide data from California Cancer Registry examined survival

outcomes in 39,434 cases diagnosed with RCC between 1998 and 2004[31]. Their studies included other racial groups in addition to whites and blacks. Their findings yet were similar. In a study comparing Asian/pacific Islanders, Hispanics, white and blacks, relative survival was found to be the worse for blacks than non-blacks. This was true despite black patients having a relatively greater percentage of localized RCC. This disparity persisted at up to 10 years of follow-up. In our study, black patients with RCC underwent surgical therapy at similar rates to white patients. Rates of surgical intervention was not available for both the Chow et al and Stafford et al studies although another study suggest blacks may be undergoing surgeries at lower rates than whites[22].

Survival results from our study are consistent with findings from a recently published study who similarly found no racial disparities in overall survival for RCC patients treated within the same health care system. Lin et al evaluated a similar sized cohort of RCC patients (2056 white and 370 black patients) treated at military treatment facilities within the Department of Defense's (DOD) health care system and found no differences in overall survival by race after adjustment for demographic, tumor and treatment factors.[35]

This consistency with our findings is noteworthy given the differences between our study population and that of Lin et al, which only included active-duty military personnel, retirees, and dependents. Despite the DOD health care system eliminating many barriers to access to care, patients frequently have supplemental health insurance and may receive some medical services outside the military system. Lin and colleagues also evaluated only overall survival while we focused on DSS, a much more important measure of biologic aggressiveness. In a population with significant differences in age and comorbidity, an analysis of overall survival alone may mask potential racial differences in disease biology

that can influence prognosis. Lin et al study only included patients with clear-cell RCC. Other subtypes were excluded on grounds of insufficient numbers. Given that papillary subtype is significantly more common in black patients, we believe that our approach of including all subtypes, particularly papillary subtype, provides a more complete assessment.

While our study and Lin's did not demonstrate a racial disparity in survival among black patients with RCC, we must acknowledge that our cohort, despite equivalent access to care, is rather homogenous in many respects to the subjects in the other studies. The larger population-based studies probably better reflect the US population as a whole. It is widely known racial disparities exist in employment, health coverage, and socioeconomic status. All black patients in this cohort likely received their healthcare coverage through their employer or their spouse's, making them more likely to be in a higher socioeconomic group. We recognize that these factors may affect treatment availability and options, which were not accounted for in our studies. It is possible that blacks in our study cohort, compared to blacks in the general population, have better access to care and are therefore being diagnosed earlier contributing to the more favorable outcomes noted in this study. Socioeconomic differences may largely explain disparities in cancer stage observed among black patients with various forms of malignancy[37,38]. Within RCC, lower socioeconomic status has similarly demonstrated an association with advanced tumor stage[39]. Not surprisingly, socio-economic status significantly influences survival for a wide variety of cancers[40].

Despite evaluating patients within a single health care system, among individuals with kidney cancer, there were significant racial differences in both patient and tumor

characteristics. The age at diagnosis of kidney cancer was significantly younger in blacks similar to other both national and multiple single-institution cohorts.[21,22,31,35].

We found that papillary RCC was nearly threefold more common in black patients compared to white patients in our cohort. This is consistent with prior single institutional and national registry cohorts that demonstrate a similar increased frequency of papillary histology in black patients[29,41]. Various factors could account for this finding. Specific risk factors for kidney cancer including hypertension, obesity, and chronic kidney disease greatly differ by race[14,16]. Limited studies have evaluated how each of these factors influence the risk of specific histologic types of kidney cancer. Genetic differences may also contribute to a different distribution of histologic subtype. Recently, genome wide association studies (GWAS) have been performed in different racial groups. Interestingly, specific kidney cancer susceptibility loci may differ in the black population [42]. Recently, black patients with clear cell RCC were shown to overexpress *BAP1* relative to whites[43]. *BAP1* overexpression is associated with more favorable pathological staging, conversely its silencing portends worse outcomes. Future case–control studies evaluating kidney cancer susceptibility should focus on specific histologic subtypes, as the genomic basis of each differs greatly[44].

The presence of comorbidities with known racial differences such as CKD and hypertension were significantly increased in blacks with kidney cancer. Both of these factors have been shown to increase kidney cancer risk and could explain some of the recent epidemiologic trends in kidney cancer incidence in blacks[14-16]. Additionally there could be a detection bias in blacks, as often patients with an unknown cause of CKD undergo renal imaging to determine etiology. This practice could lead to increased

incidental detection and skew presentation towards earlier stage disease, resulting in lead-time bias. With equal access to health care in the Kaiser System and potential early detection of CKD, racial differences in the stage of RCC perhaps may be even more pronounced than observed in other healthcare systems.

In this study, we found that unfavorable tumor histological and clinical features portend worse outcomes. We found AJCC staging to be the most powerful independent predictor of outcomes. In our multivariate analysis, patients presenting with higher AJCC stages (stages 3 and 4) carried eight times risk of disease specific mortality compared to those presenting with AJCC stages 1 and 2. This result is not unexpected given that AJCC staging is a measure of anatomical tumor extent and a well-established prognosticator of outcomes [45]. AJCC stage 3 are tumors that that are either large in size, or of any size that but extending into major veins, may have spread to nearby lymph nodes but overall still confined within Gerota's fascia. AJCC stage 4 tumors are tumors that have grown beyond Gerota's fascia, distant node involvement or metastasis.

Independent of AJCC staging, we also found tumor size to be a predictor of worse disease specific outcomes with each additional centimeter in tumor length conferring 5% increase in risk. Risk of malignancy and higher tumor grades has been shown to increase with tumor size in renal masses without diagnosis[46]. Expectedly, high tumor grades were also independent predictors of worse outcomes with grade 3 tumors carrying nearly double the risk, and grade 4 tumors carrying over the three times the risk of adverse disease specific outcomes. While male gender is a known risk factor for RCC, we found no evidence that gender was a significant prognosticator of outcome.

Our study also showed that not having surgery was a significant independent prognosticator of worse outcomes with patients who did not undergo surgery had nearly six times the risk of disease-specific mortality. We believe that most of the subjects not undergoing surgery are either patients with metastatic tumors that are not amenable to surgical treatment or people with serious comorbidities precluding them from undergoing surgery. Both of those categories of patients inherently carry a higher risk of mortality and may largely explain the vastly inferior survival associated with not having surgery.

Histologically, we found that while on univariate analysis papillary RCC subtype seems to have better outcomes compared to clear cell, histological subtype was not found to be an independent predictor of outcomes. There have been studies showing similar findings of trends towards better outcomes with papillary subtype[27,28]. We did not have sufficient data to evaluate other subtypes might influence overall outcomes

To the best of our knowledge, this is the first study examining disease-specific survival disparities in individuals with kidney cancer treated within a single regional healthcare system. We recognize that participation in such a healthcare system does not guarantee equal treatment; however, it can minimize disparate racial access. A strength of our study is that our data displays the added advantage of having cancer-specific outcomes especially since other common causes of mortality, including cardiovascular disease, also have racial disparities[47,48]. Unlike studies based only on cancer registry data, we included comorbidity data such as CKD. Inclusion of this may be critical to survival analyses as a recent paper suggests renal comorbidities account for much of the observed racial disparity[37]. Besides influencing overall survival, comorbidities may influence specific treatment decisions and similarly affect cancer outcome. Information on systemic therapy was not available at time

of recurrence; however, the equivalent rates of surgical treatment may serve as a surrogate of similar treatment at other stages of disease.

CONCLUSION

We found that within a large single healthcare system, while some patient and tumor characteristics differed between black and white patients with RCC, surgical treatment rates were similar and race was not an independent predictor of disease-specific survival. Our studies suggest that the disparities in kidney cancer survival outcomes between black and white patients noted in national registries likely result from barriers to access to care rather than disease biology. Future work should focus on identifying, understanding, and then eliminating possible racial barriers to kidney cancer treatment in other healthcare systems.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin.* 2016;66(1):7-30.
2. Chow WH, Devesa SS, Warren JL, Fraumeni JF, Jr. Rising incidence of renal cell cancer in the United States. *Jama.* 1999;281(17):1628-1631.
3. Chow WH, Shuch B, Linehan WM, Devesa SS. Racial disparity in renal cell carcinoma patient survival according to demographic and clinical characteristics. *Cancer.* 2013;119(2):388-394.
4. Gandaglia G, Ravi P, Abdollah F, et al. Contemporary incidence and mortality rates of kidney cancer in the United States. *Canadian Urological Association Journal.* 2014;8(7-8):247-252.
5. Vaishampayan UN, Do H, Hussain M, Schwartz K. Racial disparity in incidence patterns and outcome of kidney cancer. *Urology.* 2003;62(6):1012-1017.
6. Mettler Jr FA, Thomadsen BR, Bhargavan M, et al. Medical radiation exposure in the US in 2006: preliminary results. *Health Physics.* 2008;95(5):502-507.
7. Smith-Bindman R, Miglioretti DL, Larson EB. Rising use of diagnostic medical imaging in a large integrated health system. *Health Affairs.* 2008;27(6):1491-1502.
8. Kabaria R, Klaassen Z, Terris MK. Renal cell carcinoma: links and risks. *Int J Nephrol Renovasc Dis.* 2016;9:45-52.
9. Chow WH, Dong LM, Devesa SS. Epidemiology and risk factors for kidney cancer. *Nature reviews Urology.* 2010;7(5):245-257.
10. Purdue MP, Moore LE, Merino MJ, et al. An investigation of risk factors for renal cell carcinoma by histologic subtype in two case-control studies. *International journal of cancer Journal international du cancer.* 2013;132(11):2640-2647.

11. Colt JS, Schwartz K, Graubard BI, et al. Hypertension and risk of renal cell carcinoma among white and black Americans. *Epidemiology (Cambridge, Mass).* 2011;22(6):797-804.

12. Hunt JD, van der Hel OL, McMillan GP, Boffetta P, Brennan P. Renal cell carcinoma in relation to cigarette smoking: meta-analysis of 24 studies. *Int J Cancer.* 2005;114(1):101-108.

13. Kroeger N, Klatte T, Birkhäuser FD, et al. Smoking negatively impacts renal cell carcinoma overall and cancer-specific survival. *Cancer.* 2012;118(7):1795-1802.

14. Hofmann JN, Schwartz K, Chow WH, et al. The association between chronic renal failure and renal cell carcinoma may differ between black and white Americans. *Cancer causes & control : CCC.* 2013;24(1):167-174.

15. Chow W-H, Gridley G, Fraumeni Jr JF, Järvholm B. Obesity, hypertension, and the risk of kidney cancer in men. *New England Journal of Medicine.* 2000;343(18):1305-1311.

16. Hofmann JN, Corley DA, Zhao WK, et al. Chronic kidney disease and risk of renal cell carcinoma: differences by race. *Epidemiology.* 2015;26(1):59-67.

17. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in obesity among adults in the United States, 2005 to 2014. *Jama.* 2016;315(21):2284-2291.

18. Shapiro JA, Williams MA, Weiss NS. Body mass index and risk of renal cell carcinoma. *Epidemiology.* 1999;10(2):188-191.

19. Wang F, Xu Y. Body mass index and risk of renal cell cancer: A dose-response meta-analysis of published cohort studies. *International journal of cancer.* 2014;135(7):1673-1686.

20. Lipworth L, Morgans AK, Edwards TL, et al. Renal cell cancer histologic subtype distribution differs by race and sex. *BJU International.* 2014:n/a-n/a.

21. Qi P, Tsivian M, Abern MR, Passoni NM, McGinley KF, Polascik TJ. Clinicopathological characteristics and outcomes of surgically excised renal masses in African Americans. *Urologic Oncology: Seminars and Original Investigations.* 2014;32(5):555-560.

22. Berndt SI, Carter HB, Schoenberg MP, Newschaffer CJ. Disparities in treatment and outcome for renal cell cancer among older black and white patients. *J Clin Oncol.* 2007;25(24):3589-3595.

23. Chung PH, Linehan WM, Bratslavsky G. Race determines histological subtypes and stage of RCC: An analysis of the SEER database. *ASCO GU Cancer Symposium.* 2010;Abstract 314.

24. Lopez-Beltran A, Scarpelli M, Montironi R, Kirkali Z. 2004 WHO classification of the renal tumors of the adults. *European urology.* 2006;49(5):798-805.

25. Ljungberg B, Campbell SC, Cho HY, et al. The epidemiology of renal cell carcinoma. *European urology.* 2011;60(4):615-621.

26. Cheville JC, Lohse CM, Zincke H, Weaver AL, Blute ML. Comparisons of outcome and prognostic features among histologic subtypes of renal cell carcinoma. *Am J Surg Pathol.* 2003;27(5):612-624.

27. Beck SD, Patel MI, Snyder ME, et al. Effect of papillary and chromophobe cell type on disease-free survival after nephrectomy for renal cell carcinoma. *Annals of surgical oncology.* 2004;11(1):71-77.

28. Patard JJ, Leray E, Rioux-Leclercq N, et al. Prognostic value of histologic subtypes in renal cell carcinoma: a multicenter experience. *J Clin Oncol.* 2005;23(12):2763-2771.

29. Olshan AF, Kuo TM, Meyer AM, Nielsen ME, Purdue MP, Rathmell WK. Racial difference in histologic subtype of renal cell carcinoma. *Cancer medicine.* 2013;2(5):744-749.

30. Shuch B, Hofmann JN, Merino MJ, et al. Pathologic validation of renal cell carcinoma histology in the Surveillance, Epidemiology, and End Results program. *Urologic oncology.* 2014;32(1):23.e29-13.

31. Stafford HS, Saltzstein SL, Shimasaki S, Sanders C, Downs TM, Robins Sadler G. Racial/ethnic and gender disparities in renal cell carcinoma incidence and survival. *J Urol.* 2008;179(5):1704-1708.

32. Zini L, Perrotte P, Capitanio U, et al. Race affects access to nephrectomy but not survival in renal cell carcinoma. *BJU Int.* 2008.

33. Tsao CK, Small AC, Moshier EL, et al. Trends in the use of cytoreductive nephrectomy in the United States. *Clin Genitourin Cancer.* 2012;10(3):159-163.

34. Pui C-H, Pei D, Pappo AS, et al. Treatment outcomes in black and white children with cancer: results from the SEER database and St Jude Children's Research Hospital, 1992 through 2007. *Journal of Clinical Oncology.* 2012;30(16):2005-2012.

35. Lin J, Zahm SH, Shriver CD, Purdue M, McGlynn KA, Zhu K. Survival among Black and White patients with renal cell carcinoma in an equal-access health care system. *Cancer Causes & Control.* 2015:1-8.

36. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Annals of surgical oncology.* 2010;17(6):1471-1474.

37. Schwartz K, Ruterbusch JJ, Colt JS, Miller DC, Chow WH, Purdue MP. Racial disparities in overall survival among renal cell carcinoma patients with young age and small tumors. *Cancer medicine.* 2016;5(2):200-208.

38. Schwartz KL, Crossley-May H, Vigneau FD, Brown K, Banerjee M. Race, socioeconomic status and stage at diagnosis for five common malignancies. *Cancer Causes & Control.* 2003;14(8):761-766.

39. Hellenthal NJ, Bermejo CE. The role of socioeconomic status in renal cell carcinoma. Paper presented at: Urologic Oncology: Seminars and Original Investigations2012.

40. Woods L, Rachet B, Coleman M. Origins of socio-economic inequalities in cancer survival: a review. *Annals of Oncology.* 2006;17(1):5-19.

41. Sankin A, Cohen J, Wang H, Macchia RJ, Karanikolas N. Rate of renal cell carcinoma subtypes in different races. *International braz j urol : official journal of the Brazilian Society of Urology.* 2011;37(1):29-32;discussion 33-24.

42. Purdue MP, Ye Y, Wang Z, et al. A genome-wide association study of renal cell carcinoma among African Americans. *Cancer Epidemiol Biomarkers Prev.* 2014;23(1):209-214.

43. Paulucci DJ, Sfakianos JP, Yadav SS, Badani KK. BAP1 is overexpressed in black compared with white patients with Mx-M1 clear cell renal cell carcinoma: A report from the cancer genome atlas. *Urol Oncol.* 2016;34(6):259.e259-259.e214.

44. Chen F, Zhang Y, Senbabaoglu Y, et al. Multilevel Genomics-Based Taxonomy of Renal Cell Carcinoma. *Cell reports.* 2016;14(10):2476-2489.

45. Ljungberg B, Bensalah K, Canfield S, et al. EAU guidelines on renal cell carcinoma: 2014 update. *Eur Urol.* 2015;67(5):913-924.

46. Thompson RH, Kurta JM, Kaag M, et al. Tumor size is associated with malignant potential in renal cell carcinoma cases. *The Journal of urology.* 2009;181(5):2033-2036.

47. Still CH, Ferdinand KC, Ogedegbe G, Wright JT, Jr. Recognition and Management of Hypertension in Older Persons: Focus on African Americans. *J Am Geriatr Soc.* 2015;63(10):2130-2138.

48. Muntner P, Lewis CE, Diaz KM, et al. Racial differences in abnormal ambulatory blood pressure monitoring measures: Results from the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Am J Hypertens.* 2015;28(5):640-648.